

Notice of Allowability

Application No.

10/082,804

Examiner

Deborah Crouch, Ph.D.

Applicant(s)

MCCONLOGUE ET AL.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the response filed October 26, 2006 and interview summary of January 10, 2007.
2. ☒ The allowed claim(s) is/are 1,5,6,9,13-28,30-39 and 42-55.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
 5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413),
Paper No./Mail Date 1/10/07.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

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An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Ms. Elaine Chang on January 10, 2007.

1. Rewrite the following claims

1. A transgenic mouse whose genome comprises homozygous non-functional β -secretase -1 (BACE-1) genes, wherein the genes comprise a deletion in exons 4-8 of the BACE-1 gene and the mouse lacks functional BACE-1.

5. The transgenic mouse of claim 1, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene for the construct to recombine with the endogenous gene introducing the positive selection marker into the BACE-1 gene and rendering the gene nonfunctional.

6. The transgenic mouse of claim 1, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene to undergo homologous recombination with it, these segments being flanked by *frt* recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and *frt* recombination sites into the endogenous gene, and the *frt* recombination sites undergo recombination with each other thereby excising DNA between the *frt* recombination sites resulting in a deleted nonfunctional BACE-1 gene.

9. The transgenic mouse of claim 1, wherein the gene is rendered nonfunctional by homologous recombination with a targeting vector comprising a lambda KOS genomic clone of BACE-1.

13. The transgenic mouse of claim 1, whose genome further comprises a transgene comprising a DNA sequence encoding an APP having a familial Alzheimer's disease mutation.

17. The transgenic mouse of claim 13, wherein the mouse is homozygous for the non-functional BACE-1 gene.

19. A cortical cell culture derived from the transgenic mouse of claim 1, wherein the cells lack functional BACE-1.

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22. A method for screening for an inhibitor of the production of an A β peptide by a protease other than BACE-1, wherein the peptide is recognized by an antibody that recognizes residues 13-28 of A β comprising

exposing a transgenic mouse whose genome comprises homozygous non-functional BACE-1 genes, wherein the mouse lacks functional BACE-1, or a cortical cell culture derived from the mouse, wherein the cells lack functional BACE-1 to an agent; and

detecting the production of an A β with an antibody that recognizes residues 12-28 of A β ,

wherein a reduced amount of A β peptide produced in the exposed transgenic mouse or cortical cell culture relative to the transgenic mouse or the cortical cell culture not exposed to the agent is indicative of inhibitory activity.

25. A method of analyzing potential side effects for an inhibitor of β -secretase comprising

exposing a transgenic mouse whose genome comprises homozygous non-functional BACE-1 genes, wherein the mouse lacks functional BACE-1, or a cortical cell culture derived from the mouse, where the cells lack functional BACE-1 to an inhibitor of BACE-1; and

measuring whether there is a change in the level of at least one component of the transgenic mouse or cortical cell in response to the administration of the inhibitor relative to the transgenic mouse or the cell culture not exposed to the agent;

wherein a change in level of at least one component indicates a potential side effect of the inhibitor.

27. A mouse embryonic stem cell whose genome comprises a non-functional gene for BACE-1 genes, wherein the gene comprises a deletion in exons 4-8 of the BACE-1 gene.

28. The mouse embryonic stem cell of claim 27, wherein the cell is homozygous for the deletion of the BACE-1 gene.

32. The mouse embryonic stem cell of claim 27 that is homozygous for a nonfunctional BACE-1 gene lacking exons 4-8.

34. A blastocyst produced by insertion of the mouse embryonic stem cell of claim 27.

35. A method for generating a transgenic mouse comprising at least one nonfunctional BACE-1 gene, the method comprising:

introducing at least one genetic construct into a mouse embryonic stem cell, the genetic construct comprising a positive selection marker flanked by segments showing sufficient sequence relatedness to the BACE-1 gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites;

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screening for cells in which recombination has occurred between the genetic construct and the endogenous gene;

injecting the mouse embryonic stem cells, which have undergone recombination, into blastocysts to generate chimeric blastocysts;

developing the chimeric blastocysts into chimeric mice;

breeding the chimeric mice with mice of the type which provided the blastocysts to generate mice heterozygous for the nonfunctional gene of BACE-1; and

breeding the mice heterozygous for the nonfunctional BACE-1 gene with mice transgenic for flp recombinase resulting in transgenic mice whose genome comprises a nonfunctional BACE-1 gene.

36. The method of claim 35, wherein the gene is rendered nonfunctional by deletion of at least a segment of exon 1.

37. The method of claim 35, wherein the gene is rendered nonfunctional by deletion of exons 4-8.

38. A transgenic mouse comprising at least one nonfunctional BACE-1 gene, wherein the mouse or an ancestor thereof was produced by homologous recombination between an endogenous BACE-1 gene and a construct containing a positive selection marker flanked by segments showing sufficient sequence relatedness to the gene to undergo homologous recombination with it, these segments being flanked by frt recombination sites, whereby the construct recombines with the endogenous gene introducing the positive selection marker and frt recombination sites into the endogenous gene, and the frt recombination sites undergo recombination with each other thereby excising DNA between the flp recombination sites resulting in a nonfunctional endogenous BACE-1 gene.

39. The transgenic mouse of claim 38, wherein the mouse is homozygous for the nonfunctional endogenous BACE-1 gene.

42. The transgenic mouse of claim 38, wherein the gene is rendered nonfunctional by deletion of at least a segment from an exon of the gene.

43. The transgenic mouse of claim 38, wherein the gene is rendered nonfunctional by deletion of at least a segment from exon 1.

44. The transgenic mouse of claim 38, wherein the gene is rendered nonfunctional by a 165 base pair deletion of exon 1 starting from 2 base pairs past the initiating methionine and extending through the end of exon 1 replaced with an expression cassette in the targeting vector electroporated into 129 ES cells to generate the transgenic mouse.

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45. The transgenic mouse of claim 38, wherein the gene is rendered nonfunctional by deletion of exons 4-8.

46. The transgenic mouse of claim 38, whose genome further comprises a transgene comprising a DNA sequence encoding an APP having a familial Alzheimer's disease mutation.

50. A cortical cell culture derived from the transgenic mouse of claim 38, wherein the cells lack functional BACE-1.

2. Cancel claim 2

Examiner's Comment

1. The title has been changed to -Transgenic Mice Knockouts of BACE-1--.

The following is an examiner's statement of reasons for allowance: The closest prior art is PGPub document 20020157122. However, the specific deletion of exons 4-8 of the BACE-1 gene is not taught, nor is the use of frt/flp recombinase for disrupting the BACE-1 gene taught.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Deborah Crouch, Ph.D.
Primary Examiner
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January 11, 2007